REMARKS

Claims 5, 11, 16, and 23 were previously cancelled. Claims 1-4, 6-10, 12-15, 17-22, and 24-25 are pending in the application. Claims 17-18 and 25 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claim 7 has been amended as suggested by the Examiner (*See* III below).

These claims have been canceled, withdrawn, or amended without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim amended, withdrawn, or cancelled for any reason. By this, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17 (1997).

I. Previous Objections and/or Rejections

Applicants acknowledge the Examiner's withdrawal of the claim rejections under 35 U.S.C. § 103(a). OA at 2-3. Applicants further acknowledge the Examiner's withdrawal of the claim rejections under 35 U.S.C. § 112, second paragraph. OA at 3.

II. Claim Rejections – 35 U.S.C. § 112 – Scope of Enablement

The Examiner has maintained the rejection of dependent claims 7-10 and independent claim 1 for the following reason:

> [T]he specification, while being enabling for a method of identifying a candidate compound for enhancing cyclic AMP response element binding protein (CREB) pathway function by contacting host cells/cells of neural origin with a test compound and forskolin, wherein the indicator activity/CREB dependent gene expression in cells treated with forskolin and test compound is significantly increased versus that observed with cells plus forskolin alone, does not reasonably provide enablement for the identification of a candidate compound following the same steps resulting in **any difference** in CREB dependent gene expression between the groups as stated above (see claims 7-10, particularly 7(m)) (emphasis added).

OA at 3-4.

According to the Examiner, "amending claim 7(m) to recite 'significant increase' would overcome this rejection." OA at 5 (emphasis in original). In response, Applicants have made the proposed amendment to claim 7. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 7-10 and 1 under 35 U.S.C. § 112, first paragraph.

III. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 7-10 as being indefinite. OA at 6. According to the Examiner, "[c]laim 7(m) is vague and unclear for reciting the limitation 'a difference' because '[t]he instant specification teaches statistically significant increased gene expressions" and "[i]t is not clear if the difference should be significant or can be non-significant as well." OA at 6.

Applicants have amended claim 7 to replace the term "difference" with the suggested term 'significant increase,' as discussed in the preceding section. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 7-10 under 35 U.S.C. § 112, ¶ 2.

IV. Claim Rejections – 35 U.S.C. § 103 -- Obviousness

The Examiner rejected claims 1, 3-4, and 6 under 35 U.S.C. §103(a) as being unpatentable over Ying et al., in view of Tully et al., and further in view of Shoemaker et al., OA at 6-11.

The Examiner provides the following descriptions of the Ying et al., reference:

> Ying et al., teach that host cells (Calu-6 or human lung cancer cells) were transiently transfected using plasmids comprising the HREN promoter having the consensus CRE sequence (e.g. 900L, 900CRE, etc.) (Table 1; Figure 1), luciferase indicator gene, and expression vector encoding the CREB-1 transcription factor (abstract) and contacted with forskolin (Materials and Methods, page 2413, col. 2, para 2). The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector. Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

OA at 7-8 (emphasis in original).

The Examiner acknowledges, however, that Ying et al., do not teach either "the screening of a plurality of compounds that would enhance CREB function" or "repeating the method steps with a range of concentrations of the test compound." OA at 8. Instead the Examiner asserts that alleged teachings in Tully et al., and in Shoemaker et al., cover these deficiencies:

> Tully et al., teach screening assays of pharmaceutical drugs for enhancing long-term memory by activating CREB or CREB isoforms (page 4, para 4; page 5, para 2).
>
> Shoemaker et al., teach drugs for screening assays for different tumor types including neuroblastoma cells (page 2149, Table 3). Shoemaker et al., also teach that after the primary or initial screening steps of identifying test compounds, dose response assays involving 10-fold dilutions (or different concentrations) of test compound was performed (page 2146, col. 1, Drug Treatment, Materials and Methods). The reference further teaches that the complete evaluation of active compounds will involve 5-dose response experiments (i.e. will include four different concentrations as in instant claim 6) using the assay steps (or repeating the steps done with the original concentration), for determining the minimum effective concentration of the test compound (page 2150, col. 1, para 2).

OA at 8-9.

Applicants respectfully traverse. In proceedings before the USPTO, "the Examiner bears the burden of establishing a *prima facie* case of obviousness based on the prior art."[1] " To establish a *prima facie* case of obviousness, the Examiner must meet four conditions: First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior

[1] *CFMT, Inc. v. Yieldup Int'l Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003); *See In re Bell,* 991 F.2d 781, 781 (Fed. Cir. 1993) ("A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art.").

art must teach or suggest all elements in the claim.[2] Fourth, if an obviousness rejection is based on a combination of prior art references, the Examiner must show a suggestion, teaching, or motivation ("TSM test') to combine the prior art references.[3]

Following the Supreme Court's decision in *KSR v. Teleflex*,[4] the TSM test must be applied flexibly to accord with the Court's approach of *Graham v. Deere*.[5] A "flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis" in obviousness cases,[6] capturing the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[7]

A. The Combination of Cited References Fails to Teach or Suggest All Claim Limitations

The obviousness rejection is insufficient, because the combination of references fails to teach or suggest all elements of the claims. This failure reflects at least the following omissions:

1. "Suboptimal dose of a CREB function stimulating agent"

The Examiner states that "[t]he claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and *CREB function stimulating agent (forskolin)* . . ." OA at 7 (emphasis added). This statement is incomplete, however, because it fails to acknowledge that the rejected claims all require contacting host cells with a *suboptimal* dose of a CREB function stimulating agent (forskolin). As described in the instant application, a suboptimal dose of a CREB function stimulating agent allows reliable detection and measurement of effects of cognitive enhancers:

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[2] *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991); *See, also CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) ("[O]bviousness requires a suggestion of all limitations in a claim.")

[3] *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999).

[4] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

[5] *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966).

[6] *Ortho-McNeil Pharma v. Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

[7] *KSR* at 418.

> By suboptimal dose of CREB function stimulating agent is meant that amount, or dose, of CREB function stimulating agent that is required to stimulate (induce) CREB pathway function to a level that is above endogenous (basal) levels, such that a further statistically significant increase in CREB pathway function due to induction by a cognitive enhancer can be measured and the measurement is not attributable to natural cellular fluctuations or variations as a consequence of natural cellular fluctuations . . . The suboptimal dose of CREB function stimulating agent will be any concentration yielding (1) 50% or less maximal indicator activity and (2) an indicator activity above natural cellular fluctuations.

Application, p. 19, l. 22 to p. 20, l. 16.

The requirement for a suboptimal dose also underscores a guiding principle set forth in the instant application: to identify compounds "that do not enhance CREB function on their own but rather after co-stimulation with forskolin, an activator of adenylyl cyclase." Application, p. 36, ll. 7-16.

The Examiner's reliance on Ying et al., as teaching "host cells that were . . . contacted with forskolin" (OA at 8-9) is therefore deficient because the Examiner has not provided a basis in Ying et al., for host cells contacted with a *suboptimal* dose of forskolin. Nor *can* Ying et al., provide such a basis: the studies in Ying et al., are directed to quantitative studies of "the DNA sequence and transcription factor requirements for cAMP-induced transactivation of the human renin [HREN] promoter using Calu-6 cells that express human mRNA endogenously." Ying et al., p. 2412, col. 1. The results reveal, for example, that "[f]orskolin treatment alone only caused a 2-3 fold activation of the *HREN* promoter in Calu-6 cells, but nearly a 10-fold activation in JED-3 cells, which do no express rennin but are highly responsive to cAMP." *Id.* Such quantitative comparisons logically depend on full induction of cAMP signaling through optimal amounts of forskolin.

More generally, the studies in Ying et al., are focused on components acting *downstream* of cAMP, and they include the use of "[e]xpression vectors encoding the CREB-1 transcription factor, a dominant negative mutant form of CREB-1, and the catalytic subunit of protein kinase A (PKA) . . . to assess transcription factor requirements mediating the cAMP response." Ying et al., p. 2412 col. 1. This downstream focus further underscores the need for peak levels of cAMP – and hence a saturating dose of forskolin – at the top of the signaling cascade. In this regard, the

concentration of forskolin is not manipulated in any experiments in Ying et al., but is maintained at an invariant concentration (10 μM). (See Materials and Methods, *Transfections and Luciferase Assays*, p. 2143, col. 2)

In sum, the Examiner has not provided a basis for a *suboptimal* concentration of CREB function stimulating agent (forskolin), nor *can* such a basis be found in the Ying et al., reference. Likewise, there is no basis for a *suboptimal* concentration of CREB function stimulating agent (forskolin) in the Tully et al., or Shoemaker et al., references

The Examiner relies on Tully et al., for the general teaching of screening assays based on activating CREB or CREB isoforms. But Tully et al., do not disclose or suggest the instantly claimed methods for identifying cognitive enhancers, and the Examiner's citations are unavailing. The Examiner's citation to page 4, paragraph 4, for example, is directed to a behavioral assay for assessing a drug, such as one "altering the induction or activity of repressor and activator isoforms of dCREB2," but it says nothing about using a suboptimal dose of a CREB function stimulating agent. Similarly, the Examiner's citation to page 5, paragraph 2 is directed to screening assays based on modulating the relative level of CREB activator and repressor isoforms and says nothing about using a suboptimal dose of CREB function stimulating agent.

Also deficient is Shoemaker et al., which is directed to the "applicability of a human tumor colony-forming assay . . . in terms of feasibility, validity and potential for drug discovery." Shoemaker et al., p. 2145, col. 1. Moreover, the primary or initial screening step based on the tumor colony-forming assay does use of suggest using a second modulatory agent (such as forskolin), much less using a suboptimal dose of such an agent.

Ying et al., therefore fail to teach or suggest administering a suboptimal dose of a CREB function stimulating agent, and Tully et al., and Shoemaker et al., fail to correct this deficiency. On this basis alone, the cited combination of references fails to teach or suggest all limitations of the claimed inventions. Accordingly, it is respectfully asserted that the Examiner has not – and can not – establish a prima facie case of obviousness.

2. Step g) of claim 1

Step g) of claim 1 includes two requirements for selecting a test compound: (i) a significant increase of indicator activity in host cells contacted with test compound and forskolin relative to host cells contacted with forskolin alone; and (ii) no significant change of indicator activity in host cells contacted with a test compound alone relative to host cells alone.

As the only alleged support for these two limitations, the Examiner relies on Figure 6 of the Ying et al., reference:

> The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector.
>
> Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

OA at 8. This interpretation is deficient for several reasons:

First, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention."[8] Figure 6 of Ying et al., provides data from six separate experiments, but only one of these (900CRE in Calu-6 cells) provides alleged support for the Examiner's position. The Examiner reliance on a single set of data therefore fails to consider the overriding weight of contradictory data in Figure 6, as well as more general disclosures, such as the statement in the Abstract that that "over-expression of CREB-1 did *not* significantly enhance forskolin-induced human renin transcriptional activity."

Second, the 900CRE data in Figure 6 that the Examiner selectively relies upon is cell-type specific, precluding general applicability to drug screening methods – much less the instantly claimed methods. More particularly, Figure 6 reveals similar activity

[8] M.P.E.P. § 2141.02 (VI) (July 2010) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, (Fed. Cir. 1983)).

of the 900CRE reporter with CREB-1 compared with activity of the reporter alone in Calu-6 cells – but *not* in JEG-3 cells.

Third, the effect of CREB on forskolin-induced activity of 900CRE in Calu-6 cells is less than two-fold, indicating deficiencies in other components of the cAMP signaling cascade in this cell. Indeed, overexpression of PKA in Calu-6 cells increased 900CRE activity by 9.1-fold (Figure 7A), which was further increased to 19.6 fold with the addition of wild-type CREB (Figure 9A). Given these limitations of Calu-6 cells, one of ordinary skill in the art would not recognize the applicability of Ying et al., to forskolin-based screening for enhancers of CREB pathway function as defined in the instant claims.

Finally, a more fundamental pitfall – as discussed in 1.A above – overshadows the already limited findings of Ying et al., The 900CRE data in Figure 6A are not based on the use of *suboptimal* amounts of forskolin – as required by the claims. Indeed, given the less than two-fold increase in 900CRE activity upon the addition of CREB-1 (Figure 6A), there is no reasonable expectation of *any* significant increase if the assays *were* carried out in the presence of *suboptimal* amounts of forskolin. Lower concentrations of forskolin result in lower cAMP levels, reducing the likelihood of PKA translocation to the nucleus and subsequent activation of CREB. Such observations would also further dissuade the skilled artisan from using the alleged combination of Tully et al., and Ying et al., in a manner similar to the instantly claimed methods.

Ying et al., therefore do not teach or suggest step g) of the rejected claims. Moreover, this deficiency is not overcome by the Tully et al., or Shoemaker et al., references, neither of which discusses comparative studies of CRE-reporter in transfected cells. Because the cited combination of references fails to teach or suggest all limitations of the claimed invention, the Examiner has not – and can not – establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request – that the Examiner reconsider and withdraw the rejection of claims 1, 3-4, and 6 under 35 U.S.C. §103(a).

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

/djpelto Reg. No. 33754/

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Don J. Pelto
Reg. No. 33,754

Sheppard Mullin Richter & Hampton LLP
1300 I Street NW
Eleventh Floor East
Washington, D.C. 20005
Tel: (202) 772-5362
Fax: (202) 312-9415